A Convenient Synthesis of *N*-(α-Alkoxyalkyl)- and *N*-[α-(Alkylthio)alkyl]amines

Alan R. Katritzky,* Wei-Qiang Fan, Qiu-He Long
Department of Chemistry, University of Florida, Gainesville, Florida 32611-2046, USA
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Aminoalkylation of alcohols and of thiols by *N*-[1-(benzotriazol-1-yl)alkyl]amines under mild conditions give *N*-(α-alkoxyalkyl)amines **2** and *N*-[α-(alkylthio)alkyl]amines **3**, respectively, in good yields.

N-(α-Alkoxyalkyl)amines, frequently referred to as hemiaminals, are of importance both in bioorganic chemistry and in organic synthesis. They have bactericidal activity against *Staphylococcus aureus* and *Bacillus subtilis*, and fungicidal activity against *Penicillium glaucum*.[1] *N*-(α-Alkoxyalkyl)amines, especially *N*-(methoxymethyl)- and *N*-(ethoxymethyl)amines, are versatile aminoalkylation reagents. Thus, it has been long known that *N*-(α-alkoxymethyl)amines condense with electron-rich aromatic compounds to give aminoalkylation products,[2,3] and they have been widely used in preparations of aminomethylphosphonic acids,[4] [(dialkylamino)alkyl]diphenylphosphine oxides,[5] and other phosphorus compounds.[6] *N*-(α-Alkoxymethyl)amines have also been employed in the aminoalkylation of sulfinamides,[7] and as precursors of the corresponding iminium ions, which react with electron-rich olefins to form nitrogen-containing heterocycles.[8] α-(*N*,*N*-Disubstituted amino)alkyl ethers react with (trialkylstannyl)magnesium chloride to give [(dialkylamino)alkyl]trialkylstannanes.[9]

N-(α-Alkoxyalkyl)amines have been prepared by the method of McLeod and Robinson[10] or its modifications, involving direct condensations of an aldehyde with an amine and an alcohol. Primary aromatic amines also react with paraformaldehyde and sodium alkoxide to afford *N*-(alkoxymethyl)arylamines.[11] However, these methods are generally limited to formaldehyde as carbonyl component[12] and thus to the preparation of *N*-(alkoxymethyl)amines; further, the yields are usually moderate because the products suffer rapid hydrolysis.[13] Steward and Hauser reported that the condensation of benzaldehyde with secondary amines and 1-butanol in the presence of calcium sulfate and magnesium chloride gave α-aminobenzyl butyl ether in 25–67% yield, but that this reaction failed with aliphatic aldehydes.[14] Although in few case hemiaminals were obtained from secondary amines, aliphatic aldehydes and alcohols in the presence of base,[9] direct condensations are often not satisfactory, one disadvantage being the formation of symmetrical aminals.[8] Alternatively, hemiaminals have been prepared electrochemically by the anodic oxidation of tertiary amines dissolved in the corresponding alcohol.[8,15] However, the anodic method is not always convenient and most of the published results apply only to methanol solution and hence to *N*-(α-methoxyalkyl)amines.

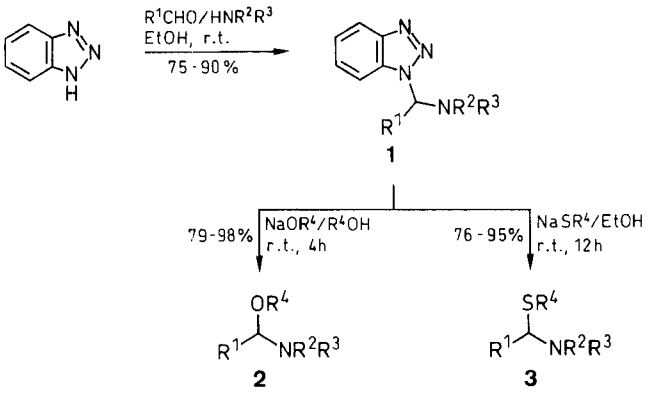
Although α-amino sulfide (*N*,*S*-acetals) structures in five- or six-membered rings are very common in heterocyclic chemistry, and are easily available,[16] open chain hemithioaminals are relatively little explored. Synthetic access to hemithioaminals and their applications have been mainly focused on formaldehyde derivatives, i.e., [(alkylthio)methyl]amines.[17] Aminomethyl phenyl sulfides are useful precursors in the preparation of (aminomethyl)trialkylstannanes[18,19] and they are prepared by the condensation of thiophenols with secondary amines and formaldehyde.[20] Far less work has been reported on hemithioaminals derived from other aldehydes. Symmetrical aminals, prepared from aromatic aldehydes and secondary amines[21] react with one molar equivalent of a mercaptan to give α-anilinoalkyl sulfides.[21] However, this method cannot be used for aliphatic aldehydes because of the easy conversion of the derived aminals to enamines if the 2-position of the aminal bears a hydrogen atom,[22] moreover the mercaptal contaminant usually complicated purification.

We have recently extended the utility of our versatile synthetic auxiliary benzotriazole[23] to amidoalkylation and demonstrated the amidoalkylation of CH-acids[24] and of electron-rich aromatic compounds[25] by *N*-[1-(benzotriazol-1-yl)alkyl]amides. *N*-[1-(Benzotriazol-1-yl)-alkyl]amides also react readily with a variety of thiols[26] and alcohols[27] under mild conditions to give *N*-acylhemithioaminals and (α-alkoxyalkyl)amides, respectively, in good to excellent yields.

In addition to this demonstrated utility for *amidoalkylation*, benzotriazole methodology also possesses considerable potential for *aminoalkylation* and we have already reported the aminoalkylation of electron-rich heterocycles with (aminoalkyl)benzotriazole.[28] We have now extended this work and the present paper describes the aminoalkylations of alcohols and of thiols by *N*-[1-(benzotriazol-1-yl)alkyl]amines which provides for the facile preparation of a wide range of *N*-(α-alkoxyalkyl)amines and *N*-[α-(alkylthio)alkyl]amines of types **2** and **3**, respectively.

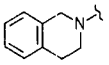
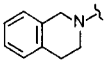
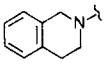
The *N*-[1-(benzotriazol-1-yl)alkyl]amines, aminoalkylation reagents **1**, were readily available from the reaction of benzotriazole, an aldehyde and an amine as previously described.[29] *N*-[1-(Benzotriazol-1-yl)alkyl]amines **1a–g** reacted with sodium alkoxides at room temperature to give the desired *N*-(α-alkoxyalkyl)amines, aminoalkylation products **2** in good yields. Compounds **2a–i** are easily hydrolyzed oils;[11,13] to avoid aqueous workup, diethyl ether was added to the mixture of compound **2** and the byproduct sodium benzotriazolate after removal of excess alcohol. The insoluble sodium benzotriazolate was removed by filtration. The essentially pure oily products were obtained simply by evaporating the ether.

These preparations are summarized in the Scheme and Table 1. In the aminoalkylation reagent **1**, R^1, R^2 and R^3 could be hydrogen, or alkyl or aryl groups. Methanol, ethanol, 1-propanol, 2-propanol and 2-butanol gave good results. However, 2,2-dimethyl-1-propanol yielded a complex mixture including only a low yield of α-alkoxylated product, probably due to the high basicity of *tert*-butoxide.



Similarly, the *N*-[1-(benzotriazol-1-yl)alkyl]amines **1** reacted with a variety of sodium salts of thiols in ethanol at room temperature to form *N*-[α-(alkylthio)alkyl]amines **3** in good yields (Table 1). Both aliphatic and aromatic thiols underwent the aminoalkylation smoothly. Hemithioaminals derived from an aliphatic aldehyde (**3f** and **3g**), aromatic and heteroaromatic aldehydes (**3a–e**) all gave good results. The workup procedure is the same as that described above for *N*-(α-alkoxyalkyl)amines.

The *N*-(α-alkoxyalkyl)amines **2** and *N*-[α-(alkylthio)alkyl]amines **3** prepared in this work, including many new compounds, were characterized by their ^1H and

1	R^1	NR^2R^3	**2**	R^1	NR^2R^3	R^4	**3**	R^1	NR^2R^3	R^4
a	H	$N(CH_2CH_2)_2O$	**a**	H	$N(CH_2CH_2)_2O$	Et	**a**	Ph	$N(CH_2CH_2)_2O$	Bn
b	H	NEtPh	**b**	H	NEtPh	Me	**b**	Ph	$N(CH_2CH_2)_2O$	Ph
c	H		**c**	H	NEtPh	Et	**c**	2-Py	$N(CH_2CH_2)_2O$	Bn
d	2-Py	$N(CH_2CH_2)_2O$	**d**	H	NEtPh	*i*-Pr	**d**	2-Py	$N(CH_2CH_2)_2O$	Ph
e	H	NHPh	**e**	H		Et	**e**	2-Py	$N(CH_2CH_2)_2O$	n-C_8H_{17}
f	Ph	NBn_2	**f**	H		*s*-Bu	**f**	*i*-Pr	NBn_2	Bu
g	Ph	$N(CH_2CH_2)_2O$	**g**	2-Py	$N(CH_2CH_2)_2O$	Me	**g**	*i*-Pr	NBn_2	n-$C_{10}H_{21}$
			h	2-Py	$N(CH_2CH_2)_2O$	Et	**h**	H	NEtPh	Bu
			i	Ph	NBn_2	*i*-Pr	**i**	H	NEtPh	Ph
			j	H	NHPh	Me				

2-Py = 2-pyridyl

Scheme

Table 1. Preparation of *N*-(α-Alkoxyalkyl)amines **2** and *N*-[α-(Alkylthio)alkyl]amines **3**

Compound	Yield (%)	Molecular Formula[a] or Lit. bp (°C)/Torr	Compound	Yield (%)	Molecular Formula[a] or Lit. bp (°C)/Torr
2a	82	55–56/1[12]	**3a**	90	$C_{18}H_{21}NOS$ (299.4)
2b	90	111–112/5[8]	**3b**	95	$C_{17}H_{19}NOS$ (285.4)
2c	98	115/25[9]	**3c**	80	$C_{17}H_{20}N_2OS$ (300.3)
2d	94	$C_{12}H_{19}NO$ (193.3)	**3d**	84	$C_{16}H_{18}N_2OS$ (286.3)
2e	88	$C_{12}H_{17}NO$ (191.3)	**3e**	85	$C_{18}H_{30}N_2OS$[c] (322.4)
2f	85	$C_{14}H_{21}NO$ (219.3)	**3f**	78	$C_{22}H_{31}NS$ (341.5)
2g	82	$C_{11}H_{16}N_2O_2$ (208.2)	**3g**	80	$C_{28}H_{43}NS$ (425.6)
2h	86	$C_{12}H_{18}N_2O_2$ (222.3)	**3h**	76	$C_{13}H_{21}NS$ (223.3)
2i	79	$C_{24}H_{27}NO$ (345.5)	**3i**	83	$C_{15}H_{17}NS$ (243.3)
2j	80	oil[11, b]			

[a] All compounds **2** and **3** are liquid; satisfactory HRMS obtained: $m/z \pm 0.0038$.
[b] Unstable and no boiling point was given in Ref. 11.
[c] Low resolution mass spectrum was obtained.

^{13}C NMR spectra and by high resolution mass spectra. The ^1H and ^{13}CNMR chemical shifts of compounds **2** and **3** and their detail assignments are summarized in Tables 2 and 3. The $NCH_2O(S)$ or NCHRO(S) signals in the ^1H NMR spectra appear as characteristic singlets or doublets at $\delta = 3.37–5.47$. The corresponding carbon signals in the ^{13}C NMR spectra appear from $\delta = 80.0$ to 97.7 for *N*-(α-alkoxyalkyl)amines **2** and from $\delta = 54.8$ to 82.9 for *N*-[α-(alkylthio)alkyl]amines **3**. Other peaks in both ^1H and ^{13}C NMR are easily assigned (Tables 2 and 3).

In conclusion, a novel procedure has been developed for the preparation of *N*-(α-alkoxyalkyl)amines and of hemithioaminals. The *N*-(α-benzotriazolylalkyl)amines used as intermediates are easily prepared from aldehydes and amines and are reasonably stable. The aminoalkylation conditions for alcohols and thiols are mild and nonacidic, also no water is produced during the reaction and this is important because these *N,O*-acetals and *N,S*-acetals are easily hydrolyzed. The workup procedure is very simple, the products are easily purified and yields mostly excellent. The methods presently described should become those of choice for the preparation of compounds of these classes.

Melting points were measured with a Kofler hot stage apparatus and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded with a

Table 2. ^{1}H NMR Spectral Data of *N*-(α-Alkoxyalkyl)amines **2** and *N*-[α-(Alkylthio)alkyl]amines **3**; δ, *J* (Hz)

Compound	NCH_2O or NCH(R)O	RR'N	OR or SR	R^1
2a	4.03 (s, 2H)	3.71 (t, 4H, *J* = 4.8), 2.66 (t, 4H, *J* = 4.8)	3.52 (q, 2H), 1.20 (t, 3H)	
2b	4.68 (s, 2H)	7.22 (t, 2H), 6.85 (d, 2H), 6.76 (t, 1H), 3.48 (q, 2H), 1.20 (t, 3H)	3.28 (s, 3H)	
2c	4.74 (s, 2H)	7.21 (t, 2H), 6.80 (d, 2H), 6.75 (t, 1H), 3.46 (q, 2H), 1.20 (t, 3H)	3.48 (q, 2H), 1.22 (t, 3H)	
2d	4.73 (s, 2H)	7.21 (t, 2H), 6.86 (d, 2H), 6.74 (t, 1H), 3.47 (q, 2H), 1.22 (t, 3H)	3.70 (m, 1H), 1.18 (d, 6H)	
2e	4.23 (s, 2H)	7.10 (m, 3H), 7.03 (m, 1H), 3.87 (s, 2H), 2.93 (m, 4H)	3.55 (q, 2H), 1.21 (t, 3H)	
2f	4.24 (s, 2H)	7.08 (m, 4H), 3.88 (s, 2H), 2.95 (m, 4H)	3.35 (d, 2H), 1.90 (m, 1H), 0.95 (d, 6H)	
2g	4.82 (s, 1H)	3.68 (m, 4H), 2.68 (m, 4H)	3.42 (s, 3H)	8.63 (d, *J* = 5.0, 1H), 7.72 (t, *J* = 2.7, 1H), 7.45 (d, *J* = 7.8, 1H), 7.23 (t, *J* = 7.2, 1H)
2h	4.90 (s, 1H)	3.69 (m, 4H), 2.67 (m, 4H)	3.60 (q, 2H), 7.25 (t, 3H)	8.62 (d, 1H), 7.72 (t, 1H), 7.50 (d, 1H), 7.22 (t, 1H)
2i	5.08 (s, 1H)	7.48 (d, 2H), 7.36–7.15 (m, 8H), 3.71 (s, 4H)	3.68 (m, 1H), 1.18 (d, 3H), 1.12 (d, 3H)	7.30–7.15 (m, 5H)
2j	4.55 (d, 2H)	7.20 (m, 2H), 6.78 (m, 3H), 4.80 (br, NH)	3.25 (s, 3H, OCH_3)	
3a	4.66 (s, 1H)	3.65 (t, 4H), 2.54 (m, 4H)	3.70 (AB system, 2H), 7.42–7.17 (m, 10H, ArH)	[a]
3b	5.35 (s, 1H)	3.68 (m, 4H), 2.78 (m, 2H), 2.62 (m, 2H)	7.62 (d, 2H), 7.40–7.15 (m, 8H, ArH)	[a]
3c	4.80 (s, 1H)	3.68 (m, 4H), 2.65 (m, 4H)	3.73 (AB system, 2H), 7.32–7.15 (m, 6H)	8.60 (d, 1H), 7.65 (t, 1H), 7.37 (d, 1H)
3d	5.47 (s, 1H)	3.65 (m, 4H), 2.75–2.55 (m, 4H)	7.52–7.41 (m, 3H), 7.30–7.13 (m, 4H)	8.60 (d, 1H), 7.65 (t, 1H)
3e	4.88 (s, 1H)	3.70 (m, 4H), 2.71 (m, 4H)	2.55 (m, 2H), 1.56 (m, 2H), 1.24 (m, 10H), 0.87 (t, 3H)	8.59 (d, *J* = 4.0, 1H), 7.68 (t, *J* = 7.8, 1H), 7.48 (d, *J* = 8.1, 1H), 7.20 (m)
3f	3.37 (d, 1H)	7.38 (d, 4H), 7.28 (t, 4H), 7.17 (t, 2H), 3.70 (AB, 4H, *J* = 14.7)	2.49 (t, 2H), 1.54 (m, 2H), 1.40 (m, 2H), 0.90 (t, 3H)	2.15 (m, 1H), 1.13 (d, *J* = 6.6, 3H), 1.07 (d, *J* = 6.3, 3H)
3g	3.38 (d, 1H)	7.38 (d, 4H), 7.29 (t, 4H), 7.17 (t, 2H), 3.70 (AB, 4H, *J* = 15.0)	2.49 (t, 2H), 1.55 (m, 2H), 1.30 (m, 14H), 0.91 (t, 3H)	2.16 (m, 1H), 1.14 (d, 3H), 1.08 (d, 3H)
3h	4.55 (s, 2H)	7.22 (t, 2H), 6.83 (d, 2H), 6.74 (t, 1H), 3.44 (q, 2H), 1.19 (t, 3H)	2.51 (t, 2H), 1.55 (m, 2H), 1.37 (m, 2H), 0.88 (t, 3H)	
3i	4.90 (s, 2H)	7.30–7.15 (m, 5H), 6.84–6.75 (m, 3H), 3.33 (q, 2H), 1.11 (t, 3H)	7.43 (d, 2H)[a]	

[a] R^1 signals overlapped with those of SR.

Varian VXR-300 (FT-mode) spectrometer at 300 MHz and 75 MHz. TMS was used as an internal reference for the ^{1}H NMR spectra. Mass spectra were obtained on an AEI MS 30 mass spectrometer. Elemental analyses were performed at the University of Florida. *N*-[1-(Benzotriazol-1-yl)alkyl]amines were prepared as previously described.[29–31] Two new benzotriazole derivatives **1c** and **1d** obtained by the same procedure,[29] are listed below.

2-[(Benzotriazol-1-yl)methyl]-1,2,3,4-tetrahydroisoquinoline (1c):
yield: 87%, mp 157–159°C (EtOH).

^{1}H NMR ($CDCl_3$): δ = 8.00 (d, *J* = 8.1 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.41 (t, *J* = 8.1 Hz, 1H), 7.38 (t, *J* = 8.4 Hz, 1H), 7.10–6.95 (m, 4H), 5.69 (s, 2H), 3.81 (s, 2H), 2.93–2.86 (m, 4H).

^{13}C NMR: δ = 144.9, 133.3, 133.0, 128.1, 127.0, 125.9, 125.6, 125.1, 123.4, 118.8, 117.7, 110.2, 68.2, 51.6, 47.7, 28.5.

$C_{16}H_{16}N_4$	calc.	C 72.73	H 6.06	N 21.21
(264.3)	found	73.05	6.23	20.96

4-[(Benzotriazol-1-yl)(pyrid-2-yl)methyl]morpholine (1d):
yield: 75%, mp 121–123°C (EtOH).

^{1}H NMR ($CDCl_3$): δ = 8.58 (d, *J* = 4.6 Hz), 8.06 (d, *J* = 8.3 Hz, 1H), 7.70 (m, 2H), 7.50 (t, *J* = 8.4 Hz, 1H), 7.40–7.20 (m, 3H), 6.70 (s, 1H, CH), 3.73 (m, 4H), 2.60 (m, 4H).

^{13}C NMR: δ = 154.3, 149.5, 145.9, 136.9, 127.2, 126.4, 123.8, 123.6, 122.8, 119.8, 111.5, 83.3 (CH), 66.6, 50.0.

$C_{16}H_{17}N_5O$	calc.	C 65.07	H 5.80	N 23.71
(295.4)	found	65.34	6.01	23.49

N-(α-Alkoxyalkyl)amines 2; General Procedure:
The *N*-(α-benzotriazolylalkyl)amine (10 mmol) was added in one portion to a solution of Na (12 mmol) in the appropriate alcohol (30 mL) at r.t. The mixture was stirred at r.t. temperature for 4 h and the excess alcohol removed under reduced pressure. Et_2O (40 mL) was added to the residue, the solid (sodium benzotriazolate) filtered off, and the ether solution dried (K_2CO_3). Removal of the solvent gave the pure compound **2** (see Scheme and Tables 1–3).

N-[α-(Alkylthio)alkyl]amines 3; General Procedure:
The thiol (10 mmol) was added to an EtOH (20 mL) solution of Na (12 mmol) at r.t. After a few minutes, the *N*-(α-benzotriazolylalkyl)amine (10 mmol) was added in one portion. The mixture was stirred at r.t. overnight. The EtOH was removed under reduced pressure, Et_2O (40 mL) was added, and the byproduct sodium benzotriazolate was filtered off. The ether solution was dried (K_2CO_3), filtered and evaporated to give pure compounds **3** (see Scheme and Tables 1–3).

Table 3. ^{13}C NMR Spectral Data of *N*-(α-Alkoxyalkyl)amines **2** and *N*-[α-(Alkylthio)alkyl]amines **3**; δ

Compound	NCHO(S)	RR'N	OR or SR	R
2a	88.3	66.9, 49.8	64.1, 15.1	
2b	83.9	147.3, 129.2, 117.9, 113.5, 45.3, 13.5	54.6	
2c	82.2	147.5, 129.1, 117.8, 113.5, 45.1, 13.4	62.4, 15.3	
2d	80.0	147.2, 129.0, 117.6, 113.7, 44.8, 13.2	67.6, 22.2	
2e	88.1	135.0, 134.3, 128.8, 126.6, 126.0, 125.6, 51.9, 47.7, 29.5	64.3, 15.4	
2f	88.3	134.9, 134.3, 128.7, 126.6, 125.9, 125.5, 51.8, 47.6, 29.4	75.8, 28.7, 19.3	
2g	97.7	66.7, 47.6	55.9	157.0, 148.8, 135.9, 122.6, 121.4
2h	96.2	66.7, 47.7	63.7, 14.9	157.7, 148.8, 135.9, 122.5, 121.5
2i	88.5	140.9, 140.2, 128.3, 127.8, 52.1	69.6, 22.8, 22.5	128.6, 128.1, 127.3, 126.9
3a	74.9	66.9, 49.2	138.3, 128.8, 128.2, 126.8, 35.3	137.1, 128.6, 127.9, 127.7
3b	82.9	66.7, 49.4	138.8, 132.0, 128.8, 126.5	136.7, 128.6, 128.0, 127.6
3c	75.6	66.8, 49.3	138.1, 128.8, 128.2, 126.7, 35.2	156.9, 148.9, 136.1, 122.7, 122.5
3d	82.7	66.4, 49.3	136.0, 132.2, 128.7, 126.6	157.5, 148.7, 136.1, 122.7, 122.3
3e	77.6	66.9, 49.9	31.6, 31.5, 29.7, 29.0, 28.8, 22.5, 14.0	158.1, 148.9, 136.2, 122.7, 122.4
3f	79.4	139.3, 128.6, 128.2, 126.8, 53.9	33.6, 32.8, 22.1, 13.7	33.4, 21.6, 21.0
3g	79.4	139.3, 128.6, 128.2, 126.8, 53.9	34.0, 31.9, 30.7, 29.6, 29.5, 29.3, 29.2, 29.0, 22.7, 14.1	33.4, 21.6, 21.0
3h	54.8	147.0, 128.9, 117.5, 113.6, 44.4, 13.5	32.2, 31.0, 22.0, 12.6	
3i	59.8	146.2, 128.8, 117.9, 113.7, 45.1, 12.7	135.7, 132.6, 129.1, 126.9	

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